CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

RIMSULFURON

Chemical Code # 3835, Tolerance # 51932
SB 950 # New A.I.

5/27/93

I. DATA GAP STATUS

Combined, rat:	No data gap; no adverse effect
Chronic toxicity, dog:	No data gap; **possible adverse effect**
Oncogenicity, mouse:	No data gap; **possible adverse effect** (not oncogenic)
Oncogenicity, rat:	See combined, rat
Reproduction, rat:	No data gap; no adverse effect
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No data gap; no adverse effect
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	Not required for this compound at this time

Toxicology one-liners are attached.

All record numbers through 121158 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T930526

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

51932-025; 116387; 2-yr combined chronic toxicity/oncogenicity; 835; Rat; E.I. du Pont de Nemours & Co., Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; 1/31/90; report #559-90 (author: D.A. Keller); rimsulfuron (IN E9636-22, 98.8% purity) was incorporated into the diet at 0, 25, 300, 3000, & 10,000 ppm; 62 rats/sex/dose; interim sacrifice at 1 yr: 10 rats/sex/dose; mortalities: after 1 yr the high dose males showed a statistically significant increase in deaths (7 vs 0 in controls @ 371 days); the lower survival rate persisted until end of 2nd yr when high control death rate eradicated the difference; no treatment-related mortality in females; males & females showed statistically significant depressions of body wt or wt gain at or during the 1st yr which persisted to some degree during the 2nd yr, but w/o statistical significance; no sustained effect on food consumption or food efficiency; no toxic signs; no ophthalmologic effects; no significant increase in tumors, gross lesions, masses, or nodules; slight effects on serum parameters at 1 and 2 yr at the high dose probably due to adaptive liver changes; relative liver & kidney wts significantly increased at 1 yr (liver only at 2 yr); NOEL (M/F) = 3000 ppm (M=121 mg/kg/day, F=163 mg/kg/day, based on liver weight and enzyme changes and male body weight changes); **no adverse effects; Acceptable. (Rubin, 2/2/93)

CHRONIC TOXICITY, DOG

****51932-050; 121158;** Chronic toxicity; 831; Dog (Beagle); Bio/dynamics Inc., East Millstone, NJ; "A Chronic (1 Year) Oral Toxicity Study in the Dog with IN E9636-22 Via the Diet"; author, J.E. Atkinson; project #89-4952; 1/4/91; rimsulfuron (IN E9636-22; 98.8% purity) was administered in the diet at 0, 50, 2500, & 10,000 ppm for 1 yr; 5/sex/dose; no deaths; no effect on food consumption; high dose females gained less weight than controls (1.9 vs.4.1 kg), though this may be due to 2 abnormally large females in the control group; corneal opacity due to lipidosis occurred in 1/5 males & 2/5 females at the high dose by 32 wks, though it had partially resolved by the time of the terminal exam; serum cholesterol and alkaline phosphatase were elevated in mid and high dose animals indicating changes in liver activity; urine volume were occasionally increased at the mid & high doses, as were liver & kidney weights & tracheal mucosal hyperplasia; **possible adverse effects:** testicular degeneration and epididymal changes; NOEL, M/F, = 1.6 mg/kg/day (50 ppm, based on cornea opacity, liver enzyme changes

and testicular degeneration); **Acceptable.** (Rubin, 3/12/93)

ONCOGENICITY, RAT

See Combined, rat

ONCOGENICITY, MOUSE

****51934-046/047; 121154/121155;** Oncogenicity; 832; Mouse; E.I. du Pont de Nemours & Co, Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; "Oncogenicity Study with IN E9636-22; 18-Month Feeding Study in Mice"; author, D.A. Keller; project #732-90; 1/18/91; rimsulfuron (IN E9636-22; 98.8%) was administered in the diet at 0, 25, 250, 2500, & 7500 ppm for 18 mo; 80/sex/dose; no compound related deaths; high dose male & female body wts and female wt gains were significantly reduced, causing significant increases in relative liver, testes, heart, & kidney wts; no changes in palpable masses, clinical observations, or hematological parameters; **possible adverse effects:** high dose females had increased eye anomalies (mostly cataracts) by the end of the expt. (18/61 vs. 5/58 in controls); high dose males had increased benign tumors (28/80 vs. 17/80 in controls, $p \leq 0.05$), decreased malignant tumors and increased incidence & severity of testicular artery and tunica degenerations (73/80 vs. 20/80 in controls, $p \leq 0.05$); NOEL (M/F) = 2500 ppm (M = 351 mg/kg/day, F = 488 mg/kg/day, based on eye anomalies and testicular artery and tunica degeneration); **Acceptable.** (Rubin, 3/22/93)

REPRODUCTION, RAT

**51932-045; 121152; Multigenerational reproductive toxicity; 834; Rat; E.I. du Pont de Nemours & Co, Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; "Reproductive and Fertility Effects with IN E9636-22 Multigeneration Reproduction Study in Rats"; author, L.S. Mullin; project #203-90; 9/12/90; rimsulfuron (IN E9636-22) was administered in the diet at 0, 50, 3000, & 15,000 ppm to P_1 rats (30/sex/group) for 74 days before breeding w/i the dose groups; compound administration to P_1 animals continued during breeding, gestation, & lactation, followed at weaning by 105 days of administration to F_1 animals before breeding w/i the dose groups (30/sex/group) to produce the F_2 generation; deaths: 1 P_1 female, 1 F_1 male, & 1 F_1 female at 15,000 ppm, and 1 F_1 female at 3000 ppm; deaths appeared to be of unrelated causes; significantly lower body wt. in high dose F_1 males (by 7 days post weaning) and F_2 pups (mid dose F_1 males & high dose F_1 & P_1 females had a similar tendency); lowered food intake in premating mid & high dose F_1 males (not P_1 males); no effect on clinical signs or reproductive indices in P_1 or F_1 adults, or F_2 pups (except for weight losses noted above); pathology exams were negative;

Maternal NOEL=15,000 ppm (1021 mg/kg/day, no effect at HDT); Reproductive NOEL-3000 ppm (204 mg/kg/day, reduced pup weight); **No adverse effect; Acceptable.** (Rubin, 3/18/93)

TERATOLOGY, RAT

** 51932-024; 116386; Teratology; 833; Rat; Haskell Laboratory for Toxicology and Industrial Medicine, Du Pont, Inc., Newark, DE; project #170-89 (author: L. Alvarez); 7/28/89; Rimsulfuron (IN E9636-22) was administered by gavage on days 7-16 of gestation; 0, 200, 700, 2000, & 6000 mg/kg; maternal effects, high dose: significantly decreased wt. gain, days 11-13, significantly reduced feed consumption, days 9-15, and altered fecal color; no significant effects on pregnancy rate, corpora lutea, nidations or resorptions/dam, or litter size; fetal weights, *in utero* survival, and incidence of variations and malformations were unaffected by the treatment; maternal NOEL = 2000 mg/kg/day, fetal NOEL = 6000 mg/kg/day; **Acceptable**. (Rubin, 1/28/93)

TERATOLOGY, RABBIT

51932-044; 121150; Teratology; 833; Rabbit; Haskell Laboratory for Toxicology and Industrial Medicine, Du Pont, Inc., Newark, DE; "Teratogenicity Study of IN E9636-22 in Rabbits" (author: L. Alvarez); project #403-89; 9/22/89; rimsulfuron (IN E9636-22; 98.8% purity) was administered by gavage on days 7-19 of gestation to animals impregnated by artificial insemination; 0, 25, 170, 500, & 1500 mg/kg; *maternal effects*; deaths: 0/20, 0/20, 0/20, 1/20, & 15/20; no effects on maternal wt. changes; significantly decreased maternal feed consumption during the dosing pd. at the 500 mg/kg/day dose (129.9 g/dam/day vs. 143.1 g/dam/day in controls, $p \leq .05$; not enough pregnant survivors at the high dose to permit interpretation); clinical observations: weakness, abortion, & cageboard staining; no fetal effects observed (*i.e.* no test article related weight changes, no malformations, no variations); maternal NOEL = 170 mg/kg/day (based on mortality); developmental NOEL > 1500 mg/kg/day (no effect at HDT); **no adverse effect, **Acceptable.** (Rubin, 3/9/93)

GENE MUTATION

51932-026; 116388; Mutagenicity; 842; CHO-K1 cells (clone BH4); E.I. du Pont de Nemours & Co., Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; 9/20/89; report #423-89; Rimsulfuron (DPX-E9636-22, 98.8% purity); doses: 0, .01, .10, .25, .75, & 1.3 mg/ml (the highest soluble dose); 2 nonactivated (18-19 hr exposure) and 2 activated (5 hr exposure) trials; after test article exposure cells were subcultured 2x over a 1 wk period before replating under selective conditions (10^{-5} M 6-thioguanine); positive controls: 0.5 mM

methanesulfonic acid (non-activated) and .015 mM DMBA (activated); neither cytotoxicity nor mutagenicity was observed in any trials; cytotoxicity tests at 1.3 mg/ml test article (the high dose) w/o S9 microsomes yielded survival rates between 91.7% and 96.3% of controls, paralleling mutation frequencies (mutants/10^6 surviving cells) between 0 and 6.9 (negative controls ranged from 0 to 6.4, positive controls from 159.3 to 218.2); in the presence of the S9 microsomes cytotoxicity at 1.3 mg/ml ranged from 68.4% to 113.4% of controls and mutation frequency ranged from 0 to 15.6 (negative controls ranged from 0 to 11.1, positive controls with DMBA from 124.0 to 190.3); **Acceptable**. (Rubin, 2/3/93)

51932-028; 116390; Mutagenicity (*S. typhimurium* reversion to histidine independence); 842; *Salmonella typhimurium*; E.I. du Pont de Nemours & Co., Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; 4/3/89; report #132-89; rimsulfuron (DPX-E9636-22, 98.8% purity); doses: 0, 50, 100, 250, 500, 750 µg/plate (high dose based on cytotoxicity); 48 hr exposure; duplicate cultures, 2 independent trials for each condition; tester strains TA1535, TA97, TA98, & TA100 exposed to sodium azide, acridine, 2-nitrofluorene, and sodium azide, respectively, as positive controls w/o S9 microsomal activation, and 2-aminoanthracene w/S9 activation; cytotoxicity seen in preliminary mutagenicity assay w/o S9 in TA1535 @ 500 µg/plate & in TA97, TA98, & TA100 @ 1000 µg/plate, w/S9 in TA1535 @ 500 µg/plate & in TA97, TA98, & TA100 @ 2500 µg/plate; no increase in back-mutation to histidine independence seen at any test article concentration regardless of the absence or presence of S9 microsomal activation; **Acceptable**. (Rubin, 2/4/93)

CHROMOSOME EFFECTS

51932-029; 116391; Structural chromosome aberration; 843; human lymphocytes; E.I. du Pont de Nemours & Co., Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; 2/4/89; report #346-89; rimsulfuron (DPX-E9636-22, 98.8% purity); doses: 0, 0.1, 0.6, 1.0, & 1.3 mg/ml (high dose based on peak solubility); 3 hr exposure; no change in # aberrations/cell, % aberrant cells, % of cells with greater than 1 aberration, or mitotic index was observed at any rimsulfuron concentration in the absence or presence of S9-mediated metabolic activation; positive controls: mitomycin C (-S9) increases the # of aberrations/cell over negative controls by 16.5-42-fold, the % abnormal cells by 10-32-fold, and the % of cells with greater than 1 aberration from 0 to 8-16%; cyclophosphamide (+S9) generated increases in # of aberrations/cell of 8.7-26-fold, % of abnormal cells of 8-22-fold, and the % of cells with greater than 1 aberration from 0 to 2-8%; no effect on any *type* of aberration was detected; both positive controls showed increases in various types of chromosomal aberrations

(particularly chromatid gaps); rimsulfuron does not elicit clastogenic changes under the conditions tested; **Acceptable**. (Rubin, 2/5/93)

51932-030; 116393; Structural chromosome aberration (micronucleus assay); 843; mouse (bone marrow polychromatic erythrocytes); E.I. du Pont de Nemours & Co., Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; 9/13/89; report #480-89; rimsulfuron (DPX-E9636-22, 98.8% purity); doses: 0, 500, 3000, & 5000 mg/kg body weight; administered by gavage; no increase in multinucleated PCE's nor any change in the mean PCE/NCE (normochromatic erythrocyte) ratio; the positive control, cyclophosphamide, induced a 9.25-fold rise compared to negative controls in mean % micronucleated PCE's among males and a 5.8-fold rise among females (no change in PCE/NCE ratio); rimsulfuron does not induce micronuclei under the present conditions; **Acceptable**. (Rubin, 2/5/93)

DNA DAMAGE

** 51932-027; 116389; Other genotoxic effects; (unscheduled DNA synthesis); 844; primary rat hepatocytes; E.I. du Pont de Nemours & Co., Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; 9/20/89; report #418-89; rimsulfuron (DPX-E9636-22, 98.8% purity); doses: 0, .0008, .004, .008, .04, .08, .4, .8, & 1.1 mg/ml (high dose close to solubility limit); 18 hr exposure; duplicate cultures, 2 independent trials; positive controls: 2-acetyl aminofluorene, .02 & .2 µg/ml; cytotoxicity, determined by assay of lactate dehydrogenase in medium after test article exposure, was minimal; no unscheduled DNA synthesis was detected at any concentration tested; mean net nuclear grains/cell (mNNG), calculated by subtracting the mean cytoplasmic grains/cell from the mean nuclear grains/cell, was always negative, even at the high dose (in Trial 1 the mNNG/cell at 1.1 mg/ml = -9.1, in Trial 2 = -3.5); positive controls ranged in the 2 trials from a mNNG/cell count as low as 17.2 at 0.02 µg/ml to as high as 48.3 at 0.2 µg/ml; **Acceptable**. (Rubin, 2/3/93)

NEUROTOXICITY

Not required for this compound at this time.